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GYNOCARDIN

A NEW CYANOGENETIC GLUCOSIDE

BY

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THE WELLCOME CHEMICAL RESEARCH LABORATORIES

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TITLES OF PUBLISHED PAPERS FROM

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1. Some new gold salts of Hyoscine, Hyoscyamine, and Atropine
2. The characters and methods of assay of the official Hypophosphites
3. Note on the mydriatic Alkaloids
4. Preparation of Acid Phenylic Salts of Dibasic Acids
5. A new method for the analysis of commercial Phenols
6. The assay of preparations containing Pilocarpine
7. Pilocarpine and the alkaloids of Jaborandi Leaves
8. A new glucoside from Willow Bark
9. The constitution of Pilocarpine Part I.
10. The composition and determination of Cerium Oxalate
11. Researches on Morphine—Part I.
12. Observations relating to the Chemistry of the British Pharmacopœia
13. Mercurous Iodide
14. The composition of Berberine Phosphate
15. A contribution to the Pharmacognosy of official Strophanthus Seed
16. The chemistry of the Jaborandi Alkaloids
17. A new admixture of commercial Strophanthus Seed
18. Researches on Morphine—Part II.
19. The constitution of Pilocarpine —Part II.
20. The chemistry of the bark of Robinia Pseud-acacia, *Linn.*
21. The anatomy of the bark of Robinia Pseud-acacia, *Linn.*
22. A soluble Manganese Citrate and compounds of Manganese with Iron
23. The chemical characters of so-called Iodo-tannin Compounds
24. The constitution of Pilocarpine —Part III.
25. A new Synthesis of *a*-Ethyltricarballylic Acid
26. The constituents of the essential oil of Asarum Canadense
27. Derivatives of Gallic Acid
28. The occurrence of Salicin in different Willow and Poplar Barks

(Continued on page 3 of cover)

XLII.—*Gynocardin, a New Cyanogenetic Glucoside.*

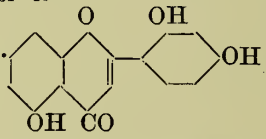
By Frederick Belding Power and Frederic Herbert Lees.

In a preliminary note it was recorded by one of us and F. H. Gornall (Proc., 1904, **20**, 137) that when the seeds of *Gynocardia odorata* (R. Br.) were crushed and brought into contact with water, a strong odour of hydrogen cyanide was developed, and this behaviour was shown to be due to the presence of a cyanogenetic glucoside, which was isolated and designated *gynocardin.* Since then we have been able to procure a large quantity of gynocardia seeds, which were specially collected for us in India, and have succeeded in isolating gynocardin in a pure state and in an amount sufficient to admit of its further study. The yield of this substance was equal to 5 per cent. of the weight of the seeds.

Gynocardin crystallises from water in colourless, glistening, prismatic needles containing $1\frac{1}{2}$ molecules of water of crystallisation, with which it readily parts at a temperature of 115°. The anhydrous substance melts at 162—163° with only slight decomposition, and has the formula $C_{13}H_{19}O_9N$. It is dextrorotatory, the anhydrous substance having in aqueous solution the specific rotatory power $[\alpha]_D^{21°} + 72{\cdot}5°$. Definite proof of the cyanogenetic nature of gynocardin is afforded by the fact that when the enzyme of the seeds, *gynocardase*, is brought into its aqueous solution, hydrogen cyanide is quickly evolved.

Until recently, the only definite cyanogenetic glucoside known was amygdalin, $C_{20}H_{27}O_{11}N$, which has the constitution

$$C_{12}H_{21}O_{10}\cdot O\cdot CH(C_6H_5)\cdot CN,$$

and is the maltose ether of benzaldehydecyanohydrin, but, in a series of researches entitled "Cyanogenesis in Plants," Dunstan and Henry have isolated and studied three other definite members of this class. They are lotusin, $C_{28}H_{31}O_{16}N$, the lotoflavin ether of maltosecyanohydrin, $C_{11}H_{21}O_{10}\cdot\underset{CN}{CH}\cdot O\cdot$  (*Phil. Trans.*, 1901, **194**, 515); dhurrin, $C_{14}H_{17}O_7N$, the dextrose ether of *p*-hydroxybenzaldehydecyanohydrin, $C_6H_{11}O_5\cdot O\cdot CH(CN)\cdot C_6H_4\cdot OH$ (*Phil. Trans.*, 1902, **199**, 399); and phaseolunatin, $C_{10}H_{17}O_6N$, the dextrose ether of acetonecyanohydrin, $C_6H_{11}O_5\cdot O\cdot C(CH_3)_2\cdot CN$ (*Proc. Roy. Soc.*, 1903, **72**, 285). It is seen that whereas, on the one hand, amygdalin, dhurrin, and phaseolunatin are sugar ethers of the cyanohydrins of substances other than sugars, lotusin, on the other hand, is an aromatic ether of a sugar cyanohydrin.

The constitution of gynocardin, the fifth member of the class of cyanogenetic glucosides which has been isolated in a pure condition, being thought of some interest, the elucidation of the question has been attempted.

When gynocardin is treated with acetic anhydride and sodium acetate, *hepta-acetylgynocardin*, $C_{13}H_{12}O_9(C_2H_3O)_7N$, is formed; it crystallises in needles melting at 118—119° and has $[\alpha]_D + 40{\cdot}4°$ in chloroform.

A most remarkable property of gynocardin, which brings it into sharp contrast with the other members of its class, is its great stability towards the usual acid hydrolysing agents. Dhurrin, for example, after heating for five minutes with dilute acid, afforded *p*-hydroxybenzaldehyde on extracting with ether, whereas with gynocardin practically no hydrolysis had taken place on heating for half an hour

with 5 per cent. hydrochloric acid, and complete hydrolysis was not effected until the solution had been heated for 9 hours. During the hydrolysis, hydrogen cyanide is generated, and the solution continually becomes darker in colour, being ultimately dark brown. Among the products of the reaction, it has been possible to identify only *d*-glucose and hydrogen cyanide, although, excluding the contingency of secondary decomposition, which undoubtedly occurs, it should have been possible to obtain, in addition to the above hydrolytic products, a substance of the formula $C_6H_8O_4$, in accordance with the equation:

$$C_{13}H_{19}O_9N + H_2O = C_6H_{12}O_6 + C_6H_8O_4 + HCN.$$

In view of the above-mentioned secondary decomposition, which was thought to be due solely to the prolonged heating necessary to effect hydrolysis, the enzyme, gynocardase, appeared to be better adapted for this purpose. Gynocardin is very readily hydrolysed at the ordinary temperature by the enzyme, but, as in the case of the hydrolysis by acid, the reaction is attended with the formation of dark-coloured resinous matter, and only glucose and hydrogen cyanide could be identified among the products.

Gynocardin readily reacts with hot barium hydroxide, with the liberation of ammonia and the formation of *barium gynocardinate*, $(C_{12}H_{19}O_9{\cdot}CO_2)_2Ba$, according to the equation:

$$C_{13}H_{19}O_9N + 2H_2O = C_{12}H_{19}O_9{\cdot}CO_2H + NH_3.$$

Gynocardinic acid, $C_{12}H_{19}O_9{\cdot}CO_2H$, prepared from its barium salt, is extremely soluble in water, and was only obtained as a nearly colourless syrup; it is dextrorotatory, and does not reduce Fehling's solution.

When gynocardinic acid is heated with dilute sulphuric acid, it is hydrolysed in accordance with the equation:

$$C_{12}H_{19}O_9{\cdot}CO_2H + H_2O = C_6H_{12}O_6 + C_6H_9O_4{\cdot}CO_2H.$$

There are formed, *d*-glucose (phenylglucosazone, m. p. 205—206°) and an *acid*, which must have the formula $C_7H_{10}O_6$. This acid could not be separated in a free state from the sugar which accompanied it, but by converting it into its *quinine salt* a small amount of the latter could be isolated in a state of purity. This salt formed needles, melting at 224° with decomposition, and on analysis gave numbers agreeing fairly well with the formula $C_{20}H_{24}O_2N_2,C_7H_{10}O_6$.

The facts from which we draw a conclusion respecting the structure of gynocardin are as follows:

(1) It has the formula $C_{13}H_{19}O_9N$.

(2) It gives a hepta-acetyl derivative.

(3) It is hydrolysed by dilute acids or the enzyme, giving *d*-glucose, hydrogen cyanide, and a third substance.

(4) It is hydrolysed by baryta, giving gynocardinic acid,

$$C_{12}H_{19}O_9 \cdot CO_2H,$$

and ammonia.

(5) Gynocardinic acid, on treatment with acid, gives *d*-glucose and an acid.

From the foregoing facts, it follows that gynocardin is the *d*-glucose ether of the cyanohydrin of a substance which may be either a trihydroxyaldehyde, $C_5H_4(OH)_3 \cdot CHO$, or a trihydroxyketone,

$$C_5H_5(OH)_3 : CO.$$

Since it has been impossible to isolate this substance, and as the quinine salt of its corresponding carboxylic acid was not obtained in an amount sufficient for the further investigation of the latter, its actual constitution could not be determined.

In accordance with the above view, the constitution of gynocardin can be represented by one of the following formulæ:

$$C_5H_4(OH)_3 \cdot \underset{\substack{| \\ CN}}{C}H \cdot O \cdot C_6H_{11}O_5 \text{ or } C_5H_5(OH)_3 : \underset{\substack{| \\ CN}}{C} \cdot O \cdot C_6H_{11}O_5 .$$

Gynocardinic acid may then be expressed as follows:

$$C_5H_4(OH)_3 \cdot \underset{\substack{| \\ CO_2H}}{C}H \cdot O \cdot C_6H_{11}O_5 \text{ or } C_5H_5(OH)_3 : \underset{\substack{| \\ CO_2H}}{C} \cdot O \cdot C_6H_{11}O_5 .$$

Experimental.

Estimation of the Hydrogen Cyanide afforded by the Seeds of Gynocardia Odorata (R. Br.).

For this purpose, 25 grams of the seeds were divested of the shells, and the kernels, weighing 17·7 grams, ground to a powder, which was allowed to remain in contact with water (100 c.c.) in a tightly-corked flask for 3 days. The liberated hydrogen cyanide was then driven over by steam, collected in a dilute solution of potassium hydroxide, and estimated by titration with a decinormal solution of silver nitrate, of which 20·5 c.c. were required, whence $HCN = 0·63$ per cent. in the kernel and 0·44 per cent. in the entire seed.

Isolation of Gynocardin, $C_{13}H_{19}O_9N, 1\frac{1}{2}H_2O$.

Four kilograms of the powdered seeds were first extracted with cold petroleum for the complete removal of the fatty oil, and then with 95 per cent. alcohol. On the removal of the alcohol, a dark syrupy residue resulted, which soon formed a paste, consisting chiefly of

a crystalline substance, which was separated from the mother-liquor at the pump. In order to remove the adhering syrupy mother-liquor, the crystalline cake was digested for several minutes with warm ethyl acetate, and again collected by filtration, when it was obtained in a nearly white condition. A further amount of the crude glucoside can readily be obtained from the syrupy alcoholic mother-liquor by first mixing it with prepared sawdust, drying the mass, and then extracting it with ethyl acetate, which slowly removes the glucoside. The whole of the crude glucoside was then dissolved in water, the solution digested with animal charcoal, and the colourless liquid concentrated under diminished pressure to the consistency of a syrup, which, after a short time, formed a hard cake of colourless crystals. This was drained and subsequently dried on porous earthenware. Two hundred grams of the perfectly white, crystalline glucoside were thus obtained. For analysis, the whole was again crystallised from water, and obtained in two successive crops (*a*) and (*b*), consisting of glistening, colourless, prismatic needles. These were dried on porous earthenware in the air. The water of crystallisation was determined by heating the substance at 115° until the weight was constant, and this is not attended by any decomposition of the glucoside. The analyses and determinations of the specific rotatory power were all conducted with the anhydrous substance.

(*a*) 0·7381 lost 0·0560 H_2O. $H_2O = 7·6$.
0·1465 gave 0·2500 CO_2 and 0·0760 H_2O. C = 46·5 ; H = 5·8.
0·2071 ,, 0·3568 CO_2 ,, 0·1058 H_2O. C = 46·9 ; H = 5·7.

A solution of 0·5341 in water, made up to 25 c.c., gave, in a 1 dm. tube, $a_D + 1°33'$, whence $[a]_D^{21°} + 72·5°$.

(*b*) 0·6856 lost 0·0464 H_2O. $H_2O = 6·8$.
0·1865 gave 0·3213 CO_2 and 0·0985 H_2O. C = 47·0 ; H = 5·9.

A solution of 0·4497 in water, made up to 25 c.c., gave, in a 1 dm. tube, $a_D + 1°18'$, whence $[a]_D + 72·3°$.

The portion (*b*) was again crystallised from water, and the recrystallised substance dried on porous earthenware in the air, and analysed as before.

0·9568 lost 0·0764 H_2O. $H_2O = 8·0$.
0·2279 gave 0·3934 CO_2 and 0·1166 H_2O. C = 47·1 ; H = 5·7.
0·6900 ,, 24·2 c.c. nitrogen (over KOH sol., sp. gr. 1·3) at 16° and 775 mm. N = 4·2.
$C_{13}H_{19}O_9N,1\frac{1}{2}H_2O$ requires $H_2O = 7·5$.
$C_{13}H_{19}O_9N$ requires C = 46·8 ; H = 5·7 ; N = 4·2 per cent.

It will be observed that the amount of water initially contained in

(*b*) was less than in (*a*), but that after recrystallisation the percentage of water was increased. The explanation of this is, that when the substance is allowed to separate slowly from a not too concentrated solution it always contains the larger amount of water, but when the conditions are the converse of these, smaller amounts of water are always found.

The molecular weight of gynocardin was very kindly determined for us by Dr. Barger, by his microscopical method (Trans., 1904, **85**, 286).

A solution containing 0·130 gram of anhydrous gynocardin in 1·878 grams of water was found to be isotonic with a solution of cane sugar of the mean concentration of 73·3 grams of the latter in 1000 grams of water:

$$M = \frac{0{\cdot}130 \times 1000}{1{\cdot}878} \times \frac{342}{73{\cdot}3} = 323$$

$C_{13}H_{19}O_9N$ requires M = 333.

It was thus shown that gynocardin crystallises in general with $1\frac{1}{2}$ molecules of water, and that the anhydrous substance has the formula $C_{13}H_{19}O_9N$.

Anhydrous gynocardin melts at 162—163° with slight decomposition; it is very sparingly soluble in all the usual organic solvents except alcohol, in which it readily dissolves on warming, and from which it slowly separates in small needles.

Gynocardin is best crystallised from water, in which it is readily soluble, even in the cold, and from a concentrated solution it separates in glistening, colourless, prismatic needles. It reduces Fehling's solution. No precipitate is formed when either lead acetate or subacetate is added to its aqueous solution. It gives no coloration with ferric chloride or with concentrated sulphuric or nitric acid.

Gynocardin is only slowly hydrolysed by boiling 5 per cent. hydrochloric or sulphuric acid; it is readily attacked by gynocardase, the enzyme contained in the seeds (p. 357), and by emulsin, with generation of hydrogen cyanide, but is not hydrolysed either by diastase or by the animal ferments, ptyalin, pepsin, and pancreatin. In this connection, it may also be stated that gynocardin has been ascertained to be devoid of any appreciable physiological action.

Hepta-acetylgynocardin, $C_{13}H_{12}O_9(C_2H_3O)_7N$.

Gynocardin was dissolved in an excess of hot acetic anhydride, a small amount of anhydrous sodium acetate introduced, and the mixture boiled on a sand-bath during 40 minutes. On shaking with water, the acetyl derivative separated as a white, flocculent precipitate; this was washed, dried on porous earthenware, and recrystallised, first from a

mixture of ethyl acetate and light petroleum, then from a mixture of chloroform and petroleum, and finally from the former mixture of solvents, without any appreciable change in the melting point.

Hepta-acetylgynocardin forms aggregates of fine, white needles melting at 118—119°.

0·1532 gave 0·2907 CO_2 and 0·0736 H_2O. C = 51·8 ; H = 5·3.
0·1672 „ 0·3180 CO_2 „ 0·0808 H_2O. C = 51·8 ; H = 5·4.
$C_{13}H_{12}O_9(C_2H_3O)_7N$ requires C = 51·7 ; H = 5·3 per cent.

A solution of 0·4740 in chloroform, made up to 25 c.c., gave, in a 1 dm. tube, $\alpha_D + 0°46'$, whence $[\alpha]_D + 40·4°$.

Hydrolysis of Gynocardin by Dilute Acids. The Formation of d-*Glucose.*

Gynocardin is only very slowly hydrolysed by heating with 5 per cent. hydrochloric or sulphuric acid, and the reaction is always attended with the formation of a dark secondary product, even when the operation is conducted in an atmosphere of carbon dioxide. In experiments in which two portions of gynocardin of 10 grams each were heated, in the one case for 2 hours on a water-bath with 100 c.c. of 5 per cent. hydrochloric acid, and in the other by boiling for 4 hours with 5 per cent. sulphuric acid, it was possible to recover some unchanged gynocardin, hydrolysis having been far from complete, even with these prolonged periods of heating. The following experiment represents the result of the complete hydrolysis of gynocardin with hydrochloric acid.

Twenty grams of gynocardin were dissolved in 200 c.c. of 5 per cent. hydrochloric acid and the solution heated on a water-bath. Hydrogen cyanide was not present in the liquid until the heating had been in progress for half an hour. After 7 hours' heating, when the solution smelt strongly of hydrogen cyanide and had become brown in colour, steam was passed through it. It then became apparent that hydrolysis had not been complete, for it was necessary to continue the distillation until 2½ litres of liquid had collected before all the hydrogen cyanide was removed. The residual liquid, which contained the non-volatile products of the completely hydrolysed glucoside, was very dark brown, considerable secondary decomposition appearing to have taken place. This solution was neutralised with sodium hydroxide, concentrated considerably under diminished pressure, and extracted with ether, but nothing was removed by the latter. It was therefore mixed with previously extracted sawdust, the mass dried, and extracted with ether, ethyl acetate, and ethyl alcohol respectively. The ether and ethyl acetate extracted nothing, but from the alcoholic extract there

separated a quantity of well-formed crystals; these were collected and recrystallised from water, when they were found to consist of a double compound of *d*-glucose and sodium chloride. By recrystallisation from methyl alcohol, it was possible to remove some of the salt and obtain crystals containing 85 per cent. of the sugar. That this crystalline substance consisted chiefly of *d*-glucose was definitely proved by the formation from it of a phenylglucosazone melting at 206°, and by the determination of its specific rotatory power, when the phenomenon of mutarotation was observed, the value falling to one-half of that first recorded.

A solution of 0·672 in water, made up to 10 c.c., gave, in a 1 dm. tube, $\alpha_D + 5°52'$, and, after the addition of a trace of alkali, $\alpha_D + 2°57'$, whence $[\alpha]_D + 87·3°$ and $+43·9°$ respectively.

Action of Barium Hydroxide on Gynocardin. Formation of Gynocardinic Acid, $C_{12}H_{19}O_9·CO_2H$.

Ten grams of gynocardin were dissolved in a hot solution of 20 grams of barium hydroxide in 100 c.c. of water. Ammonia was immediately evolved, and the solution was therefore boiled until the latter was entirely expelled. The excess of barium was then completely removed as carbonate, and the clear, faintly-coloured solution of the barium salt concentrated to a syrupy consistency. By adding alcohol, again evaporating, and repeating this operation several times, the *barium gynocardinate* formed a hard, white, crystalline cake. For analysis, it was heated at 115—120°.

0·5845 gave 0·1605 $BaSO_4$. Ba = 16·2.

$C_{26}H_{38}O_{22}Ba$ requires Ba = 16·4 per cent.

Gynocardinic acid was prepared from the barium salt by exact removal of the barium by sulphuric acid. A strongly acid liquid was thus obtained. This, on concentration under diminished pressure, afforded a nearly colourless syrup, which, even on standing for several days, showed no tendency to crystallise. Gynocardinic acid does not reduce Fehling's solution; its aqueous solution is dextrorotatory.

Action of Dilute Sulphuric Acid on Gynocardinic Acid. Formation of d-*Glucose and an Acid.*

A quantity of gynocardinic acid was heated for several hours on a water-bath with dilute sulphuric acid. The latter was then exactly removed as barium sulphate and the faintly-coloured acid liquid concentrated under diminished pressure. A syrup was thus obtained

which would not crystallise. In addition to the *acid*, it also contained *d*-glucose, for it readily afforded a phenylglucosazone melting at 205°.

In an attempt to separate the acid, the warm aqueous solution of the above syrup was neutralised by the addition of freshly precipitated quinine. The aqueous solution of the quinine salt and glucose, after digesting with animal charcoal, was concentrated considerably under diminished pressure. From the viscous liquid, a small amount of a crystalline salt slowly separated. This was first recrystallised from water, in which it was extremely easily soluble, and then from methyl alcohol, from which it separated in glistening needles, melting at 224° with decomposition. It was dried at 115° and then analysed:

0·1659 gave 0·3884 CO_2 and 0·0988 H_2O. C = 63·8; H = 6·6.
$C_{20}H_{24}O_2N_2,C_7H_{10}O_6$ requires C = 63·0; H = 6·6 per cent.

Although the amount of *quinine salt* thus obtained was too small for further investigation, its isolation is of value, since it affords direct proof that by the hydrolysis of gynocardinic acid a carboxylic acid is formed in addition to *d*-glucose.

Isolation of the Hydrolytic Enzyme, Gynocardase.

One kilogram of the finely-ground seeds was first extracted with cold light petroleum for the removal of the fatty oil, and subsequently digested with water at the ordinary temperature for about 24 hours. To the filtered liquid, about twice its volume of alcohol was added, and, after standing for some hours, the precipitate was collected on a filter, washed with alcohol, and dried in a vacuum over sulphuric acid. When dry, it could be reduced to a light brown powder. The yield corresponded to 2 per cent. of the weight of the seeds.

Gynocardase responds to most of the usual tests for proteid substances. As already stated, it readily hydrolyses gynocardin, and it also hydrolyses amygdalin. It appears, however, to have no action on potassium myronate, in this respect differing from the enzyme contained in *Taraktogenos* seeds (Trans., 1904, **85**, 841).

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continued

29. THE CONSTITUENTS OF COMMERCIAL CHRYSAROBIN
30. THE CONSTITUENTS OF AN ESSENTIAL OIL OF RUE
31. METHYL β-METHYLHEXYL KETONE
32. INTERACTION OF KETONES AND ALDEHYDES WITH ACID CHLORIDES
33. THE ANATOMY OF THE STEM OF DERRIS ULIGINOSA, *Benth.*
34. THE CHEMISTRY OF THE STEM OF DERRIS ULIGINOSA, *Benth.*
35. THE CONSTITUTION OF PILOCARPINE —Part IV.
36. PREPARATION AND PROPERTIES OF DIMETHYLGLYOXALINE AND DIMETHYLPYRAZOLE
37. THE ELECTROLYTIC REDUCTION OF PHENO- AND NAPHTHO-MORPHOLONES
38. CHEMICAL EXAMINATION OF KÔSAM SEEDS (BRUCEA SUMATRANA, *Roxb.*)
39. COMPARATIVE ANATOMY OF THE BARKS OF THE SALICACEÆ—Part I.
40. THE CONSTITUTION OF CHRYSOPHANIC ACID AND OF EMODIN
41. THE CONSTITUTION OF EPINEPHRINE
42. A LÆVO-ROTATORY MODIFICATION OF QUERCITOL
43. THE CONSTITUENTS OF THE ESSENTIAL OIL OF CALIFORNIAN LAUREL
44. SOME DERIVATIVES OF UMBELLULONE
45. THE CONSTITUENTS OF CHAULMOOGRA SEEDS
46. THE CONSTITUTION OF CHAULMOOGRIC ACID—Part I.
47. CHEMICAL EXAMINATION OF CASCARA BARK
48. CHEMICAL EXAMINATION OF GYMNEMA LEAVES
49. THE RELATION BETWEEN NATURAL AND SYNTHETICAL GLYCERYLPHOSPHORIC ACIDS
50. GYNOCARDIN, A CYANOGENETIC GLUCOSIDE
51. PREPARATION AND PROPERTIES OF 1 : 4 : 5—TRIMETHYLGLYOXALINE
52. THE CONSTITUTION OF PILOCARPINE —Part V.
53. THE CONSTITUTION OF BARBALOIN—Part I.
54. THE CONSTITUENTS OF THE SEEDS OF HYDNOCARPUS WIGHTIANA, *Blume*, AND OF HYDNOCARPUS ANTHELMINTICA, *Pierre*
55. THE CONSTITUENTS OF THE SEEDS OF GYNOCARDIA ODORATA, *R.Br.*
56. THE SYNTHESIS OF SUBSTANCES ALLIED TO EPINEPHRINE